

REMARKS

**0. Claim Amendments**

0.1. Claims 1, 4 and 11-14 have been amended in response to the indefiniteness rejection.

Claim 1 contemplates a "bifunctional complex" which comprises a display molecule attached to an identifier oligonucleotide. It is disclosed that the display molecule may be assembled from building blocks comprising a chemical entity and an anti-codon, and the anti-codons subsequently hybridized (annealed) to the complementary codons of the identifier oligonucleotide. P25, L2-10. In this instance, the attachment is noncovalent. Alternatively, the building blocks may be chemically or enzymatically ligated. P25, L17-24. This results in a covalent attachment.

Claim 1 likewise contemplated that the target was associated with a target oligonucleotide. As explained at P64, L22-P65, L2, this has the advantage that if there is more than one target, the target oligonucleotide serves to identify the target bound by a particular bifunctional complex. (See new claim 88.) The association between the target and the target oligo may be covalent or non-covalent, see P65, L13-15.

For the sake of convenience, we have amended claim 1 to refer to the association of the target and the target oligo as a "target complex". This is simply for convenience of reference and does not further define the character of the association.

Claim 1 also contemplates that the members of the library of bifunctional complexes are mixed with the one or more target complexes, thus giving them given the opportunity to bind. Such binding is of course expected to be between the display molecule in the bifunctional complex, and the target in the target complex.

Such binding results in what might be termed a "super-complex", of the form

(Identifier oligo ~ display molecule) ~ (target ~ target oligo),

wherein the first parenthetical is the bifunctional complex, the second parenthetical is the target complex, and ~ symbol can be either a covalent or a non-covalent interaction. This super-complex is called a "conjugate" in claim 75.

Finally, claim 1 contemplates that the target oligo is coupled to the identifier oligo. While we appreciate that since coupling includes covalent coupling, that it could be said that there is an indirect coupling of the target oligo to the identifier oligo as a result of the binding of the target by the display molecule, it is clearly envisioned that this coupling is an additional connection. Hence, claim 1 now recites "said coupling being in addition to the indirect coupling resulting from said binding of the display molecule to the target...."

Per P72, L10-15, the coupling may be by hybridizing of complementary portions of the target oligo and the identifier oligo. (See new claim 85).

Per P70, L12-14, the coupling may be by hybridizing at least part of the target oligo and at least part of the identifier oligo to a complementary oligo (cp. "connector oligo" at P71, L28-31). This would be a non-covalent coupling if no further manipulation occurred.

Per P70, L16-19, the coupling may be by chemical (see new claim 86) or enzymatic (see new claim 87) means, i.e., covalent.

Additionally, there could be first a non-covalent coupling and then a covalent coupling, per P71, L28-P72, L8.

Claim 17 has been cancelled because it did not appear to further limit claim 1. Antecedent basis problems in claims 5 and 6 have been corrected. Claim 9 has been amended to excise language of preference; the preferred limitations are now made mandatory in new dependent claims 83 and 84. In claim 71, step xvii) should have been step f), as is apparent from step xvi); this has been corrected.

Withdrawn claims 69-71 and 74 have been amended to improve the case for rejoining them, see section 1 below.

Claim 75 has been amended, and claim 76 cancelled, since if the display molecule had binding affinity for the target as required by claim 75, it would be bound to the target as required by 76.

Originally filed claims 43, 46, 47, 48, 53, 54, 56, 60, 62 (claim numbering as in PCT Pamphlet), cancelled prior to the first action on the merits, have been reinstated (without multiple dependency) as new claims 89-97. However, claim 89 (replacing 43) recites "and" (a preferred embodiment) instead of "and/or", and is now dependent on new claim 85; claim 90 (replacing 46) is dependent on new claim 87; claim 93 (replacing 53) is dependent on 85.

## **1. Unity**

1.1. The office action is incomplete in that it fails to respond to our July 29 2009 traversal of the species restriction requirement mailed February 4, 2009. The examiner has neither withdrawn the species restriction requirements, nor made them final (with a response to our traversal).

1.2. In response to the various species restrictions, we made the following elections on July 29, 2009 (a "/" indicates, if preceding election not sufficiently specific, then we elect whatever follows):

- A. Category of Molecular Target: protein/enzyme/kinase.
- B. Nature of Association Between Target and Target Oligo: covalent linkage/cleavable covalent linkage.
- C. Bifunctional complex: A complex of the elected display molecule and the identifier oligo, the latter being elected to be a series of naturally occurring nucleotides/DNA.
- D. Display Molecule: benzodiazepines.
- E. Chemical Entities Used to produce the display molecule: benzodiazepine and C1-6 alkyl/methyl.
- F. Link between display molecule and identifier oligo: PC Spacer phosphoramidite.

(For further explanations of the elections, see the Election with Traverse.)

All of the new claims are generic to or otherwise read upon the elected species for all of species restrictions A-F.

1.3. The examiner urges that claims 69-82 are directed to an independent or distinct invention from that of the originally presented claims, and hence has withdrawn these claims from consideration under the doctrine of constructive election as drawn to an unelected invention.

This case is the national stage of a PCT application, hence PCT unity rules apply. Consistent with this, the examiner cites 37 CFR 1.475, pertaining to unity of invention during the national stage. However, we wish to point out that the "independent or distinct invention" standard referred to in the first paragraph of page 2 is the standard from the domestic restriction practice and is not the relevant criterion for a national stage case.

Rather, the relevant criterion is the one referred to in 1.475(a), i.e., whether the claims relate to "one invention only or to a group of inventions so linked as to form a single general inventive concept".

It appears to us that the examiner has misunderstood the role of 1.475(d). This does not say that there cannot be unity between claims to different processes. Rather, it says that if the multiple processes are not linked to form a single general inventive concept, per 1.475(a), that it is the first-claimed process that would be considered the main invention. It should be borne in mind that 1.475 applies not only during the national phase, but also when the USPTO is acting as the International Searching Authority or the International Preliminary Examining Authority. If an application claimed multiple processes that lacked unity under 1.475(a), the ISA/US would search only the first-mentioned process, and it would be up to applicant to decide whether to pay additional search fees to have the other processes searched.

The examiner has failed to make any clear analysis under 1.474(a) or, to be more particular, under PCT Rule 13 and the relevant PCT administrative instructions. Under PCT rule 13.2, the key question is whether the claims to the multiple processes recite, as limitations, "one or more of the same or corresponding special technical features," those in turn being defined as features which, singly or in combination, define a contribution over the prior art.

Instead, the examiner merely assumes that independently claimed processes (methods) lack unity per se. The closest the examiner comes to any kind of analysis is to assert (in our opinion, erroneously) that "the withdrawn claims appear to have been filed in U.S. Application No. 12/095,778, which further supports the understanding that claims 69-82 are directed to alternative inventions than those of claims 1-20."

1.1. We have conducted a proper analysis under 1.475 and PCT Rule 13. Claim 1, as examined, was drawn to

1. A method for identifying display molecule(s)

having affinity towards molecular target(s),  
comprising the steps of

    mixing one or more molecular target(s)  
associated with target oligonucleotide(s) and a  
library of bifunctional complexes, each bifunctional  
complex of the library comprising a display molecule  
attached to an identifier oligonucleotide, which  
codes for said display molecule,

    coupling to the target oligonucleotide(s) the  
identifier oligonucleotide of complexes comprising  
display molecules binding to the target, and

    deducing the identity of the binding display  
molecule(s) and/or the molecular target(s) from the  
coupled product between the identifier  
oligonucleotide(s) and the target  
oligonucleotide(s).

In turn, claim 69 is an independent claim drawn to

69. A method for generating a conjugate  
comprising a molecular target associated with a  
target oligonucleotide and a bifunctional complex  
comprising a display molecule attached to an  
identifier oligonucleotide which codes for said  
display molecule,

wherein said display molecule has an affinity for  
and is bound to said molecular target,

said method comprising the steps of [steps (i)-(xvi)  
are then recited]

The "mixing" and "coupling" steps of claim 1 in fact  
generates a conjugate such as that recited in the preamble of

claim 69. In this regard, we direct the examiner's attention to steps xiii) and xiv) of claim 69:

xiii) reacting in a yet further reaction step e)

the molecular target associated with a target identifier oligonucleotide as generated in step vi) and the display molecule associated with a display molecule identifier oligonucleotide as generated in step xii), thereby generating a conjugate comprising a molecular target display molecule reaction product,

xiv) optionally coupling the molecular target identifier oligonucleotide and the display molecule identifier oligonucleotide,

We appreciate that depending on the interpretation of "coupling" in claims 1 and 69, that the invention of claim 69 may share the special technical features of claim 1 only when optional step xiv) of claim 69 is carried out, but clearly that means that claim 69 should have been examined at least to the extent that step xiv) is performed.

Likewise, the decoding step of claim 1 corresponds to optional step xvi) of claim 69:

still further optionally decoding said coupling of said molecular target identifier oligonucleotide and said display molecule identifier oligonucleotide, or a part thereof, thereby identifying the scaffold chemical units and the chemical entities which have participated in the synthesis of the molecular target and/or the display molecule

Hence, we must conclude that claim 69 should have been examined at least to the extent that steps xiv) and xvi) were deemed to have been carried out. Claim 69 has now been amended to make these steps mandatory.

Claim 70 is directed to "A method for generating a complex comprising a molecular target and a final display molecule comprising more than one molecular part...."

The products of claim 70 steps vii) and xiii) both appear to be bifunctional complexes within the meaning of claim 1. Steps xv) and xvi) then mix and couple these to a target, and step xviii) then decodes. Hence, we must conclude that claim 70 should have been examined at least to the extent that steps xvi) and xviii) were carried out. Claim 70 has now been amended to make these steps (as well as step xvii)) mandatory.

Claim 71 is directed to "A method for generating a second generation library comprising a molecular target associated with a target oligonucleotide and a bifunctional complex comprising a modified display molecule attached to an identifier oligonucleotide which codes for said modified display molecule...." This time, the first generation bifunctional complex is complexed to the target in step xiii) and the second generation bifunctional complex is complexed to the same target in step xvi), with decoding in step xx). It is perhaps less clearcut that steps iii) and xvi) embrace the coupling contemplated by claim 1. However, if such coupling is not required to distinguish the art, then claim 71 could still have the same special technical features as claim 1 (i.e., the other limitations of claim 1) and should be examined at least to the extent that step xx) was carried out. Claim 71 has now been amended to make this step mandatory.

Claim 72 is drawn to



A method for second generation-library driven proximity selection comprising the steps of

- i) generation of a first library,
- ii) generation of a second generation library based on the knowledge obtained from use of said first library, and
- iii) use of said second generation library for proximity selection, ....

Step (b) explicitly calls for "mixing a bifunctional complex comprising a displayed molecule and an identifier oligonucleotide with said molecular target linked to said target oligonucleotide". Step (d) calls for "ligation of said target sequence with said identifier oligonucleotide to generate a ligated product", which appears to be a form of coupling within the meaning of claim 1. There is no decoding step, but step (f) requires "selection of ligated products that contain display molecules that possess affinity for the target molecule".

Hence, claim 72 has unity if the first two features of claim 1 (mixing and coupling) are sufficient to distinguish the art.

The analysis of claim 73 is similar to that for claim 72.

Claim 74 step xvii (decoding) has been amended to make it (as well as step xv) mandatory. However, there is no direct coupling of the target oligo to the two identifier oligos.

Claim 75 is drawn to

A conjugate comprising a molecular target associated with an oligonucleotide and a bifunctional complex comprising a display molecule attached to an

identifier oligonucleotide which codes for said display molecule, wherein said display molecule has binding affinity towards said molecular target

This claim has a product/process of making relationship to claim 69. Hence, if claim 69 has unity with claim 1, it follows that 75 has unity with 69 and should also be joined under 1.475(b)(1).

1.2. We next address the examiner's assertion that claims 69-82 are each identical to one of the claims of 12/095,778 - an assertion that would be easier to test if the examiner had identified the counterpart in the '778 case of each of the instant claims 69-82.

The examiner also does not clarify whether his assertion is based on the claims of '778 as originally filed, or as currently pending. We have compared the instant claims 69-82 to the currently pending '778 claims, as a holding of provisional novelty-type double patenting would be proper against any of 69-82 that was in fact identical to a currently pending '778 claim, whereas cancelled '778 claims would be irrelevant to such inquiry.

The current claims set for 12/095,778 (Franch=6A) is that set forth in the preliminary amendment filed December 15, 2008. Franch=6A claim 1 is directed to "A method for the synthesis of a bifunctional complex...." Claims 2-5, 13, 14, 16, 18, 20, 22, 24, 38-40, 43, 59-62, 89-95, 112 and 113 are dependent on claim 1.

Franch=6A claim 116 is directed to "A method for the synthesis of a plurality of different bifunctional complexes...." Claims 117-119 are dependent on 116.

Franch=6A claim 124 is directed to "A method for identifying a molecule", making use of the library produced by the method of claim 116. Claims 125, 130, 131, and 133 are dependent on 124.

Franch=6A claim 140 is directed to a bifunctional complex per se, and 161 to a library of different bifunctional complexes according to claim 140.

The instant claim 69 is plainly not identical to any of the '778 claims because none of those claims are to the production of the conjugate to a target and a bifunctional complex. The closest they come is '778 claim 124, which requires identifying a molecule by subjecting the library to "assaying conditions", partitioning, and then decoding a partitioned complex.

Those "assaying conditions" could, of course, comprise expose the library to a target, however '778 claim 124 is substantially shorter than the instant claim 69 and quite plainly is not identical in scope.

Claims 80-82 are dependent on 69 and do not duplicate any '778 claim.

The instant claim 70 is directed to "A method for generating a complex comprising a molecular target and a final display molecule...." This complex is of target and final display molecule, not a bifunctional complex of a display molecule and an identifier oligonucleotide. Again, it is not identical in scope to any of the '778 claims.

The instant claim 71 is directed to "A method for generating a second generation library comprising a molecular target associated with a target oligonucleotide and a bifunctional complex...." and hence is distinguishable by virtue of the reference to the tatget.

Claims 72 and 73 are both for "A method for second-generation library driven proximity selection..." They require (1) generation of a first library and (1) generation of a second generation library. While '778 claim 116 contemplates library synthesis, it does not require synthesis of two libraries.

Claim 75 is directed to a conjugate of a target (with associated oligo) and a bifunctional complex, per se, and

plainly differs from '778 claim 140 as the latter is drawn to just the bifunctional complex. Claims 76-79 are dependent on 75.

1.3. We must emphasize that even if the examiner were correct - i.e., that any of claims 69-82 was a duplicate of a claim in (or formerly in?) The '778 case, we do not see the relevance of this to the determination of unity. A case may present multiple independent claims to methods without this constituting an admission that these lack unity under the standards of PCT Rule 13. All it means is that the applicant felt that the simultaneous presentation of multiple independent claims was necessary in order to fully protect the invention.

Counsel has, in another prosecution, presented multiple independent composition claims that differed in terms of how a certain prior art embodiment was disclaimed. This resulted in claims that were strongly overlapping, but not identical. The examiner restricted, counsel petitioned against the restriction, and the petition was granted.

## **2. Objections to the Specification -- pursuant to 37 CFR 1.77(b) (8)**

This application presents Figs. 1, 2A-2D, 3A-3C, 4-10, 11A-11B, 12, 13A-13B. There is a "Brief Description of the Figures" on pages 112 to 113 and a "Detailed description of the figures" on pages 113 to 119, but these both discuss only Figs. 1-10 (the Detailed Description" discusses the subparts of 2 and 3). However, on page 43, lines 18-23, there is a Brief Description of Figs. 11-13.

It appears that through the foregoing, 37 CFR 1.77(b) (8) is satisfied.

The arrangement of application elements set forth in

1.77(b) is recommended not mandatory (note the "should"). Nonetheless, we have added the section title BACKGROUND OF THE INVENTION per (b)(6) and SUMMARY OF THE INVENTION per (b)(7), and consolidated the description of the drawings after the SUMMARY OF THE INVENTION per (b)(8).

If the examiner is of the opinion that there is a feature of the drawings that must be mentioned here, but isn't, the examiner should specifically identify what is missing so that this can be addressed.

### **3. Claim rejections under 35 USC 112**

3.1. We have amended claim 1 to make it clearer that the target oligo is coupled to the identifier oligo.

In addition, we have now explicitly recited that one first provides at least one "target complex" (the name is arbitrary), which is the previously recited target associated with the target oligo", and a library of bifunctional complexes, and then mixes the library with the target complex so the bifunctional complexes can attempt to bind to the target complex(es). Such binding is, of course, by the display molecule of the bifunctional complex to the target of the target complex.

3.2. Claims 4, 11, 12, 13 and 14 have been amended to cure the problem of lack of antecedent basis.

### **4. Claim rejections under 35 USC 103**

The Examiner has produced the argument that the present claims are unpatentable over Szostak in view of Rabani. Also, the Examiner acknowledges that Szostak does not *explicitly* teach that the target is fused to a nucleic acid. Applicant concurs with the Examiner's assertion in this respect. Also, Applicant submits that Szostak also does not *implicitly* teach

a target fused to a nucleic acid.

Applicant further submits that Rabani -- neither explicitly, nor implicitly -- teaches that the target is fused (covalently or noncovalently) to a nucleic acid. Hence, there would appear to be no motivation for combining Szostak and Rabani -- and even if the case that a skilled artisan would be motivated to combine the two references, the combination would not produce the claimed invention. Rabani is not directed to a library versus library screening.

The Examiner makes reference to Fig. 26 in Rabani. This figure illustrates a method wherein, in step A), a mixture of bi-functional complexes in the form of "Peptide/NA#1"; "Peptide/NA#2"; and "Peptide/NA#3" is mixed with a target -- in the form of "Peptide analyte #1" -- wherein this "Peptide analyte #1" is not linked or fused to a nucleic acid. In step B, "Peptide/NA#1" binds to "Peptide analyte #1" - again without a "target oligonucleotide" linked or fused to "Peptide analyte #1". In step C, the nucleic acid part of "Peptide/NA #1" hybridizes to a complementary probe in a discrete location of a solid support. Accordingly, nowhere does Fig. 26 disclose the step of coupling a "target oligonucleotide" and an "identifier oligonucleotide", cf. citation thereof in claim 1 on file.

A brief legend to Fig. 26 can be found in section [0093] in Rabani and this brief legend confirms that the coupling which is illustrated in Fig. 26 is between the nucleic acid part of a "chimeric composition" (i.e. the nucleic acid (NA) portion of "Peptide/NA#1"; "Peptide/NA#2"; and "Peptide/NA#3", respectively, and a complementary probe (sequence) linked to the solid support).

The detailed description does not contain any reference to Fig. 26, but sections [0250] to [0253] would appear to be directed to Fig. 26 -- although [0250] cites "Fig. 28" in the last line of the section.

In summary, the combination of Szostak and Rabani does

not arrive at the claimed invention -- even in the event that there existed a motivation to combine the two references.

In our preferred embodiments, our "coupling" is a covalent coupling (obtained e.g. by a ligation step or by a nucleotide extension reaction), and the coupling is also a direct coupling between the two respective oligonucleotides -- as illustrated e.g. in Figs. 1 to 10 of the present application as filed.

The term "covalent" appears in Rabani only in a few places (see e.g. [0245] and [0247]) -- and in each instance the term is used to signify the link between a peptide molecule and the corresponding oligonucleotide -- nowhere is the term "covalent" used to signify that two oligonucleotides (each linked to different library members) can be linked together.

Even if the examiner finds claim 1 to still be obvious, consideration should be given to whether e.g. new claims 85-87 distinguish the art.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.  
Attorneys for Applicant

By: 

Iver P. Cooper  
Reg. No. 28,005

624 Ninth Street, N.W.  
Washington, D.C. 20001  
Telephone: (202) 628-5197  
Facsimile: (202) 737-3528  
IPC:lms  
G:\ipc\g-i\hoib\Thisted1A\thisted1a.ptoamendment.wpd